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Time series analyses of breathing patterns of lung cancer patients using nonlinear dynamical system theory

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Abstract
The underlying requirements for successful implementation of any efficient tumour motion management strategy are regularity and reproducibility of a patient’s breathing pattern. The physiological act of breathing is controlled by multiple nonlinear feedback and feed-forward couplings. It would therefore be appropriate to analyse the breathing pattern of lung cancer patients in the light of nonlinear dynamical system theory. The purpose of this paper is to analyse the one-dimensional respiratory time series of lung cancer patients based on nonlinear dynamics and delay coordinate state space embedding. It is very important to select a suitable pair of embedding dimension ‘m’ and time delay ‘\tau’ when performing a state space reconstruction. Appropriate time delay and embedding dimension were obtained using well-established methods, namely mutual information and the false nearest neighbour method, respectively. Establishing stationarity and determinism in a given scalar time series is a prerequisite to demonstrating that the nonlinear dynamical system that gave rise to the scalar time series exhibits a sensitive dependence on initial conditions, i.e. is chaotic. Hence, once an appropriate state space embedding of the dynamical system has been reconstructed, we show that the time series of the nonlinear dynamical systems under study are both stationary and deterministic in nature. Once both criteria are established, we proceed to calculate the largest Lyapunov exponent (LLE), which is an invariant quantity under time delay embedding. The LLE for all 16 patients is positive, which along with stationarity and determinism establishes the fact that the time series of a lung cancer patient’s breathing pattern is not random or irregular, but rather it is deterministic in nature albeit chaotic. These results indicate that chaotic characteristics exist in the respiratory waveform and techniques based on state space dynamics should be employed for tumour motion management.
1. Introduction

The goal of radiotherapy is to deliver a tumouricidal dose of radiation to the target tissue while avoiding the neighbouring healthy and sensitive tissues as much as possible. In spite of the apparent simplicity of this goal, it is estimated that a considerable fraction of cancer patient death is caused by local failure (Webb 1997). This implies that conventional radiotherapy does not successfully eradicate all tumour cells in the immediate vicinity of the primary tumour. Thames et al (1992) have postulated that a 20% increase in dose will result in a readily detectable increase in tumour control probability (TCP). Such gains in TCP are the basis of conformal radiotherapy. Despite the benefits from target dose conformality and normal tissue sparing, intensity-modulated radiation therapy (IMRT) is known to be more susceptible to tumour motion compared with conventional treatment techniques (Suh et al 2009). Due to patients’ non-periodic breathing patterns, the planned dose is very often not delivered as intended. Manoeuvring the moving targets during radiotherapy is still an open question. To minimize motion effects, several techniques such as treatment of a motion envelope (van Herk 2004), the average intensity projection of a motion envelope (Ehler and Tomé 2008) and modulation of the dose rate (Ehler and Tomé 2009), gating (Kubo et al 2000, Vedam et al 2001, Li et al 2006, Wink et al 2008), direct tracking (Shirato 1999, Takai et al 2001, Berbeco et al 2004, Britton et al 2005, Wiersma et al 2008) and indirect tracking (Kubo and Hill 1996, Ozhasoglu and Murphy 2002) and breathing synchronization (Tewatia et al 2006, Zhang et al 2003) methods have been developed or are under development. As pointed out in AAPM report 91 (Keall et al 2006) lack of knowledge of real-time tumour position and issues related to system latencies add to the problem of tumour motion management. In particular for synchronization methodologies, the underlying requirements are regularity and reproducibility of a patient breathing pattern.

The problems of tumour motion compensation in lung cancer patients based on breathing and tumour position prediction ahead in time have been addressed. Most of these methods are based on simple harmonic functions or sinusoidal model-based predictive filters. Such models have difficulty capturing transients and highly irregular patterns in the breathing signal. Murphy et al (2002) and Isaksson et al (2005) showed that adaptive filters and neural networks (NN) with least-mean-square (LMS) updated coefficients performed better than the Kalman filter-based algorithm for non-stationary breathing signals. Nonlinear NN with a single neuron (Yan et al 2006) and multiple neurons (Sharp et al 2004) have also been proposed. In Murphy and Dieterich (2006), an LMS algorithm and a nonlinear NN were tested on highly irregular breathing. The nonlinear NN, with weights updated using the LMS algorithm, was in general found to have a better prediction performance and more robustness than the LMS filter. Ruan et al (2006) used subspace projection methods (Ruan et al 2006) and concluded the study with hope to design plan-dependent irregularity indices for more promising results. Recently, the same group used the semi-periodicity in a breathing pattern using Poincare sectioning methodology for real-time profiling of respiratory motion (Ruan et al 2009).

Performance of any predictive model can be assessed based on four main qualities: accuracy, stability, robustness and generality. Most of the linear and nonlinear methods mentioned above fail to predict accurately when the system latency is greater than 200 ms. Murphy and Dieterich (2006) have shown that prediction accuracy is strongly influenced by the characteristics of the individual breathing patterns. The configuration parameters, generally considered to be design criteria, as explained by Sharp et al (2004) are not easy to determine and one set of configuration/design parameter cannot be used to fit all patients. Thus, generality relates to the ability of a filter design to handle a wide range of signal inputs without requiring...
specialized tuning for different signal types. Most of the techniques described above do not fit well to all types of patients.

None of the above methods really delve deep into the underlying mechanism governing respiratory breathing. Breathing is a neurophysiological process, which is controlled by rhythmical centres which are not irregular or random (Rybak et al 2007). Almost all studies described above have found that predictors fail for highly ‘irregular’ patients. It is important to note that the terms ‘irregular’, ‘random’ or ‘complex’ have been used when none of the conventional methods provide acceptable results. Murphy and Dieterich (2006) used dispersion in the spectral power around dominant frequency to quantify the complexity and irregularity of breathing signals. However, just viewing the spectral complexity does not guarantee to reveal complete picture of the underlying breathing dynamics. It is thus important to understand these differences/complexities in the respiratory signal from a new perspective by considering the breathing as a dynamical system. This will not only help in designing patient-specific prediction models based on their day-to-day breathing pattern, but also potentially be more accurate for longer latencies as explored in areas other than radiation therapy.

In this paper nonlinear time series analysis methods were applied to quantify the breathing pattern of lung cancer patients. Respiratory time series data of 16 patients, randomly selected, were analysed. From this pool of patients, a breathing time series data was randomly chosen, here after referred to as the ‘sample patient’. In order to illustrate the concept of this paper detailed results were shown for this patient’s breathing time series data and similar tests were performed for other remaining 15 patients and results are tabulated. Unlike in other fields (Hu et al 2009, Ryan and Sarson 2008, Carniel and Di Cecca 1999, Shang et al 2009, Shang and Kamae 2005), work has not been presented in which the breathing mechanism of lung cancer patients has been analysed in its entirety because one only acquires scalar time series data of this higher dimensional system. In this work, we propose a methodology for analysing a patient’s respiratory waveforms based on nonlinear dynamics by considering the respiratory system as a dynamical system.

1.1. Before analysing

Before we embark on analysing the scalar time series using chaotic nonlinear dynamical system theory, we would like to define the following terms ‘state space’ ‘chaos’, ‘attractor’, and ‘chaotic attractor’ that are used in this paper. The state space of a dynamical system is the set of all possible states of a dynamical system; each state of the system corresponds to a unique point in the state space. The number of degrees of freedom of a dynamical system is the dimension of its state space, i.e. the number of variables needed to completely describe dynamics of the system. In this paper, we denote this underlying dimension of the system by ‘d’.

While there are no definitions of ‘chaos’ that is universally accepted, most investigators would however agree that the following working definition of chaos given by Strogatz (1994) contains the key ingredients: chaos is an aperiodic long-term behaviour in a deterministic system that exhibits a sensitive dependence on initial conditions.

An attractor A is a closed set that is (a) invariant, i.e. any trajectory starting in A stays in A, and (b) attracts an open set of initial conditions and (c) is minimal, i.e. there is no proper subset of A that satisfies condition (a) and (b). A chaotic attractor is an attractor that exhibits a sensitive dependence on initial conditions. In the literature, chaotic attractor and strange attractor have been used interchangeably. For a thorough introduction to nonlinear dynamics and chaos the reader is referred to the excellent textbook by Strogatz (1994) and for
an introduction to nonlinear time series analysis, to the excellent monograph by Kantz and Schreiber (2004).

It is rather intuitive to understand how one can reconstruct a state space for a system once the differential equations describing the system are known. However, how does one obtain this state space from a given scalar time series. This question is answered by Takens’ embedding theorem, which guarantees that if the embedding dimension is larger than $2d + 1$, the reconstruction of the dynamical system from the scalar time series in a $2d + 1$ Euclidian space is topologically equivalent to the original dynamical system whose state space dimension is $d$. We will revisit this in some detail in section 2.1.

In particular, one can reconstruct the whole state space of a system from a single scalar time series measurement of sufficient length using an appropriate delay coordinate embedding. An appropriate time delay ‘$\tau$’ and embedding dimension ‘$m$’ were computed using mutual information and the false nearest neighbour (FNN) methods, respectively, which is explained in detail in section 2.1. Once the state space using a sufficiently high embedding dimension that allows one to ‘disentangle’ the attractor has been constructed, one can use tools from nonlinear system theory to further analyse the time series. The first and most crucial task in dynamical analysis of time series data is establishing stationarity. Stationarity of a scalar time series is an important requirement for using any nonlinear dynamical analysis. The appropriate method of checking the stationarity of a given scalar time series is based on checking full joint probability distribution rather than just checking the constancy of its lower order moments, namely mean and variance. So in this paper, we have used a cross-prediction method (explained in detail in section 2.2) proposed by Schreiber (1997). This method determines the degree to which information about one segment of a given scalar time series allows prediction of another segment of the time series. If the time series is stationary and each segment is sufficiently long, equal cross prediction should be possible, because each segment will be governed by the same joint probability distribution. Secondly, before applying any other techniques, it is important to establish that the dynamics generated by the scalar time series is indeed deterministic in nature, rather than stochastic. We have used the algorithm by Kodba et al (2005), a slight variation of an algorithm by Kaplan and Glass (1992), to determine if the time series is generated by a deterministic system. This is explained in section 2.3. Once determinism in given data has been established, we moved on to see if a positive largest Lyapunov exponent (LLE) exists, indicating that the given scalar time series exhibits a sensitive dependence on initial conditions, i.e. is chaotic rather than irregular or random in nature. The definition of LLE and method on how to determine the same is explained in section 2.4. A flow diagram for the above-explained methodology for the analysis of breathing patterns using nonlinear dynamics is shown in figure 1. Lastly, visualization of such higher dimensional attractors, especially when the dimension is greater than 3 can be very challenging. Recurrence plots (RPs) can reduce these higher dimensional data to two dimensions that can help one visualize the structure of these higher dimensional data. RPs, a graphical method, first introduced by Eckmann et al (1987), were originally designed to locate recurring patterns in experimental data sets. This is explained in section 2.5. It can be used to give insight into periodicities, determinism and non-stationarity of a signal. We have used the RP methodologies to reveal dynamical behaviours not obvious in the fundamental time series of lung cancer patients to demonstrate the usefulness of such tools in overall motion management of lung tumours for radiotherapy. Our analysis of breathing time series of lung cancer patients using tools from nonlinear dynamics hints at their utility in the design of algorithms aimed at controlling chaos and improving the accuracy and long-term prediction data of lung tumour motion and augment existing motion management techniques.
2. Materials and methods

2.1. Respiratory system as a dynamical system

In this work, we consider the respiratory system as a nonlinear dynamical system. A dynamical system is called dissipative if the state space volume containing the initial conditions is on average contracted under the dynamics. Dissipative nonlinear dynamical systems are typically characterized by the presence of attracting fixed points or attractors. A stable attractor is a set of points in state space that is approached by all trajectories once transients have died away that started from an open set of points known as the basin of attraction. A defining attribute of an attractor on which the dynamics is chaotic is that it displays a sensitive dependence on initial conditions.

Typically a nonlinear dynamical system can be characterized by delay state space diagrams or state space plots that relate the current state of the system $x(t_{i+1})$ at time $t_{i+1}$ denoted as $x_{i+1}$ from here on, to the preceding value of the state of the system $x_i$ at time $t_i$. The discrete set of
values of states of the dynamical system is given by \[ \{x_i\}_{i \in T} ; T = \{1, 2, \ldots, N\} \]
is referred to as a time series of the dynamical system. Such scalar time series data of respiratory signals were obtained using the real-time position management system (RPM)\(^\text{TM}\) (Varian Medical Systems, Palo Alto, CA), which uses an infrared camera to track a reflective marker on the patient’s chest. The sample rate of the RPM system is 30 frames s\(^{-1}\). Suppose \(x_i\) are scalar samples acquired at times \(t_i\) separated by a fixed time interval \(t_s\), hence \(t_i = t_0 + i \cdot t_s\), yielding the scalar time series \(S\):

\[
S = \{x_i\}_{i \in T} ; \quad T = \{1, 2, \ldots, N\}.
\]

Using the Takens’ embedding theorem (Takens 1981) a time delay embedding in an \(m\)-dimensional Euclidian space can be generated using the scalar time series \(S\) that preserves the topological properties of the attractor. In particular, Takens’ embedding theorem guarantees that if \(m \geq 2d + 1\), the time delay reconstruction of the attractor formed by the \(m\)-dimensional state space vectors,

\[
x_i = (x_{i-(m-1)\tau}, x_{i-(m-2)\tau}, \ldots, x_{i-\tau}, x_i),
\]

is topologically equivalent to the original attractor whose state space is \(d\)-dimensional. In equation (1), \(x_i\) are the original scalar time series data points and ‘\(\tau\)’ is the time delay. For a discrete scalar times series \(S\), ‘\(\tau\)’ does not have units, but is simply an integer-valued quantity whose value is indicated by what sample value the signal is advanced or delayed. To reconstruct the attractor successfully using equation (1), the first crucial parameter to determine is the time delay, \(\tau\), which preserves the underlying dynamics of the analysed system in the state–space reconstruction. The choice of the delay time, \(\tau\), has to fulfill two competing requirements for a proper state space reconstruction. First, the time interval \(\tau\) must be large enough to guarantee that the information at each of the two consecutive elements in the state vector is different enough to allow one to consider them as two different coordinates of the reconstructed space, i.e. reduce the redundancy error. Second, \(\tau\) has to be small enough to prevent the loss of the deterministic relation between consecutive elements, i.e. keep the irrelevance error small. Hence, the chosen time should result in an optimal trade-off between redundancy and irrelevance. To estimate an optimal time delay, we have used the method of mutual information function (Fraser and Swinney 1986), since it yields an attractor reconstruction that is as spread out as possible.

While Takens’ embedding theorem guarantees that an embedding dimension of \(2d + 1\) is sufficient to reconstruct an attractor of dimension \(d\), one finds however in practice that this can often be accomplished by means of a much smaller embedding dimension. In particular the method of FNN (Kennel et al 1992) allows one to estimate the minimal number of dimensions necessary to ‘disentangle’ the attractor. Therefore, we have chosen the embedding dimension, \(m\), based on a global FNN analysis (Kennel et al 1992). The method is based on the assumption that an attractor of a deterministic dynamical system folds and unfolds smoothly with no sudden irregularities in its structure. A global FNN analysis incrementally increases \(m\) until the number of FNN approaches zero. FNN are defined as sets of points that are very close to each other in dimension \(m = k\) but are not in dimension \(m = k + 1\). However, usually the time series data obtained using experimental techniques are contaminated by measurement noise and hence the dimension \(m + 1\) may be regarded as optimum when the percentage of false neighbours for points in the \(m + 1\) dimensional state space is less than a certain threshold which is set as an arbitrary number depending on the type of data one is dealing with.
2.2. Stationarity test

In very broad terms, a stationary process has the property that the mean, variance and autocorrelation structure do not change over time. A formal definition of stationarity as defined by Kantz and Schreiber (2004) is that a system is called stationary if all joint probabilities of finding the system at some time in one state and at some later time in another state is independent of time within the observation period.

Once we prove that time series is stationary, we can use conventional tools of nonlinear dynamical system theory for further analysis to calculate parameters such as the LLE. We have used the cross-prediction error statistic proposed by Schreiber (1997). Given a time series and a value $x_i$ at a discrete time $k$, it is possible to predict the value of the time series $\Delta n$ time steps ahead. Root mean square (RMS) prediction error is defined as

$$\delta = \sqrt{\frac{1}{N} \sum_{k=1}^{N} (\hat{x}_{k+\Delta n} - x_{k+\Delta n})^2}$$

where $N$ is the number of predictions made. $\hat{x}_{k+\Delta n}$ is the predicted value at time $k + \Delta n$. This is compared with the true value $x_{k+\Delta n}$.

Now that prediction error is defined, we would like to explain a simple prediction schema following Kantz and Schreiber (2004) to estimate the next measurement $\hat{x}_{N+\Delta n}$. For the scalar time series $S = \{x_k\}_{k \in T} : T = \{1, 2, \ldots, N\}$, if we want to predict the next measurement $x_{N+\Delta n}$, $\Delta n$ time steps ahead of $x_N$, one first forms a $\varepsilon$-ball around the corresponding delay vector $x_N$ that we denote by $B_\varepsilon(x_N) = \{x_k : \|x_k - x_N\| < \varepsilon\}$, where $\varepsilon$ is of the order of the resolution of the measurements. Then for all close neighbours $x_i \in B_\varepsilon(x_N)$ of $x_N$, one looks up the corresponding individual ‘predictions’ $x_k + \Delta n$, which are given by the last components of the delay vectors $x_N$, cf equation (1). The prediction $\hat{x}_{N+\Delta n}$ is then the average of these individual predictions:

$$\hat{x}_{N+\Delta n} = \frac{1}{|B_\varepsilon(x_N)|} \sum_{x_k \in B_\varepsilon(x_N)} x_k + \Delta n,$$

where $|B_\varepsilon(x_N)|$ is the number of elements in the $\varepsilon$-ball around $x_N$ in embedding space. In case one does not find any neighbours of $x_N$ that are closer than $\varepsilon$ one increases $\varepsilon$ until one does find some.

Now, we use the cross-prediction error in order to reveal differences between various non-overlapping segments of the time series $\{S_i\}_{i=[1,2,\ldots,l]}$ to test if the time series data are stationary. The idea of cross prediction is simply to use one segment $S_i$ of the data to make predictions in another segment $S_j$ of the data. For each point in $S_j$, we perform predictions according to equation (3), by searching for neighbours in $S_i$. Hence, we use $S_i$ as the training set and $S_j$ as the test set. Subsequently, we evaluate the accuracy of the obtained predictions by calculating the RMS prediction error $\delta(i, j)$ according to equation (2). Here the notation for prediction error has been slightly modified to reflect on which data segments predictions were performed $S_j$, and which data set provided the neighbours $S_i$. This process is repeated for all data segments $\{S_i\}_{i=[1,2,\ldots,l]}$. Lastly, it is important to note that for $i = j$, the cross-prediction error is simply a prediction error that is expected to be minimal. Hence, we check if the dynamics that produced the second data segment is similar to the one that yielded the first data segment. If the time series is stationary and each segment sufficiently long, equal cross prediction should be possible, because each segment will be governed by the same joint probability distribution.

We used the program stationarity.exe described in Perc (2005) to calculate the cross-prediction error for the sample patient chosen. Parameter values provided to the program are the embedding delay and dimension (table 1), the number of points in each segment (500),
Close observation of the reconstructed state space plot of a sample patient breathing time series using time delay $\tau = 49$ and the embedding dimension $m = 5$ shows the presence of low level of measurement noise.

The initial $\epsilon$ (0.02), a factor for increasing the initial $\epsilon$ (1.41 for the sample patient), and the number of time steps for prediction (10). With the radius of the $\epsilon$-ball set to 0.02, there existed at least two neighbours on an average in all patient breathing traces.

2.3. Determinism Test

The reconstructed state space plot of the attractor corresponding to the breathing time series of the sample patient is shown in figure 2. To answer the question whether this sample attractor is generated by an underlying nonlinear deterministic dynamical system or by an underlying nonlinear stochastic process we have applied to it the determinism test by Kodba et al (2005) which is a variation of the algorithm introduced by Kaplan and Glass (1992). The first step in the calculation of the determinism factor, $k$, consists of dividing the embedding space into equally sized boxes. For each pass $i$ of the trajectory corresponding to the attractor, the direction of a unit vector ($e^{(k)}_i$) pertaining to box $k$ is obtained by determining the state space point where the trajectory first enters box $k$ and the state space point where the trajectory leaves box $k$. An approximation of the vector field $V_k$ in box $k$ of the state space is calculated by averaging the unit vectors obtained from all passes through the box according to

$$V_k = \frac{1}{P_k} \sum_{i=1}^{P_k} e^{(k)}_i$$

where $P_k$ is the number of passes through box $k$. Repeating this for all occupied boxes gives the desired directional approximation for the vector field of the system. The details and the software program used for this test are well described by Kodba et al (2005). In a reconstructed vector field, if none of the vectors $e^{(k)}_i$ cross, the length of average vector $V_k$ will be unity, while the crossing of any two vectors in the sum on the right hand side of equation (4) will decrease its length. Therefore, for a deterministic system the determinism factor $k$, which is the average over the lengths of all average vectors $V_k$, will be close to 1, while for a time series that results from an underlying stochastic process it will be close to 0, since many of the unit vectors will cross. For this calculation the five-dimensional embedding space was coarse.

![Figure 2](image-url)
grained into a $10 \times 10 \times 10 \times 10 \times 10$ grid. We have calculated the determinism factor $k$ for all 15 patients.

2.4. Lyapunov exponents

LEs are a measure of the expected average separation between nearby state space trajectories as the system evolves in time. The presence of a positive LE leads to the exponential divergence of nearby trajectories as the system evolves, which is the generic mechanism for generating deterministic randomness and unpredictability. Indeed, the existence of a positive LE for almost all initial conditions in a bounded dynamical system is a widely used definition of deterministic chaos, i.e. the sensitive dependence on initial conditions. For a given deterministic nonlinear dynamical system, the spectrum of LEs is a set of real numbers $\{\lambda_1, \lambda_2, \ldots, \lambda_d\}$ giving a measure of the average rate of divergence or convergence of initially nearby trajectories in state space. Since the number of LEs for a given deterministic nonlinear dynamical system equals the dimension of the state space associated with it, this spectrum of LEs can be ordered from the largest to the smallest value, $\lambda_1 \geq \lambda_2 \geq \cdots \geq \lambda_d$. Clearly, for a dissipative dynamical system not all LEs can be positive, since this would imply that the state space volume occupied by the dynamical system would expand rather than contract as time goes on, which precludes the existence of attractors. Hence, for a dissipative dynamical system the sum over the entire spectrum of Lyapunov exponents has to be negative. Once stationarity and determinism have been established, the sign of the LLE $\lambda_{\text{max}}$ allows one to ascertain whether a system exhibits a sensitive dependence on initial conditions or not, i.e. if it is chaotic or not? The LLE $\lambda_{\text{max}}$ can be defined using the following functional relationship (Rosenstein et al 1993):

$$d(t) = D_0 \exp(\lambda_{\text{max}} t),$$

where $d(t)$ is the average Euclidean distance between neighbouring trajectories at time $t$ and $D_0$ is average initial displacement between trajectories at $t = 0$. For a detailed discussion why the largest Lyapunov can be defined in this way the reader is referred to an excellent paper by Rosenstein and co-workers (1993). The algorithm proposed by Rosenstein and colleagues determines the Euclidean distance between all pairs of nearest neighbours in time delay embedding space. Thus, the distances can be tracked forward in time for all data points. When one data point of each pair hits the final length of the data set and is no longer available, that nearest neighbour pair is discarded. Analysed data sets must therefore be sufficiently long to ensure that $\lambda_{\text{max}}$ may be calculated across a desired time frame without significant attrition in the number of available nearest neighbour pairs. The logarithm of the distances between nearest neighbours are averaged at each point in time and output as a single vector of distance. This averaging of all pairs of nearest neighbours at each point in time is key to enabling calculation of $\lambda_{\text{max}}$ in finite data sets. The LLE $\lambda_{\text{max}}$ is calculated as the slope of the linear regression line defined by

$$y(i) = \frac{1}{\Delta t} \langle \ln[d_i(j)] \rangle$$

where $\Delta t$ denotes the sampling frequency, $\langle \ldots \rangle$ denotes the average over all values of $j$, and $d_i(j)$ is the distance between the $j$th pair of nearest neighbours after $i$ discrete-time steps, i.e. $i \cdot \Delta t$ seconds. The LLE $\lambda_{\text{max}}$ was calculated as the slope (via the least-squares ‘polyfit’ command in Matlab\textsuperscript{TM} from MathWorks Inc.). To convert these units to time per second, $\lambda_{\text{max}}$ was divided by average cycle time.
2.5. Recurrence plots

A fundamental property of deterministic dynamical systems and the one typical for nonlinear dynamical systems is that states, i.e. trajectories, come arbitrarily close to one another after some time, which is also called the recurrence of states. Eckmann et al (1987) have introduced a tool, with which one can visualize the recurrence of states $x_i$ in state space. A reconstructed state space does not always have a dimension that is low enough so that a graphical representation of the attractor trajectory is possible. To visualize higher dimensional state spaces ($m > j$) one can project them into special two or three-dimensional sub-spaces. RPs represent such a sub-space and enable one to investigate an $m$-dimensional state space trajectory through a two-dimensional representation of its recurrences.

The recurrence of a state at time $i$ at a different time $j$ is marked within a two-dimensional square matrix in which both rows and columns represent time. The pixel $(i, j)$ represents the Euclidean distance between the two corresponding trajectory points. This representation is called a RP. In an unthresholded RP (UTRP), the pixel lying at $(i, j)$ is grey-shaded according to the numerical value of the Euclidean distance; in a thresholded RP (TRP), the pixel lying at $(i, j)$ is black if the distance falls within a specified threshold corridor and white otherwise.

The thresholded RP can be mathematically expressed as follows:

$$R_{i,j} = \Theta(\varepsilon - \|x_i - x_j\|), \quad x_i \in \mathbb{R}^m, \quad j = 1, \ldots, N$$

where $N$ is the number of $x_i$ considered, $\varepsilon$ is the threshold distance, $\|\bullet\|$ denotes the Euclidean norm and $\Theta$ is the Heaviside function.

As pointed out above, the purpose of RPs is the visual inspection of higher dimensional state space trajectories. The view on RPs gives hints about the time evolution of these trajectories. The RPs exhibit characteristic large-scale and small-scale patterns, the former were denoted by Eckmann et al (1987) as typology and the latter as texture. The typology offers a global impression that can be characterized as homogeneous, periodic, drift and disrupted. Detailed information on qualitative analysis can be found in Eckmann et al (1987). Homogeneous RPs are typical of stationary and autonomous systems in which relaxation times are short in comparison with the time spanned by the RP. An example of such an RP is that of a random time series. Oscillating systems have RPs with diagonal-oriented, periodic recurrent structures (diagonal lines, checkerboard structures). For quasi-periodic systems, the distances between the diagonal lines are different. Abrupt changes in the dynamics as well as extreme events cause white areas or bands in the RP. A diagonal line occurs when a segment of the trajectory runs parallel to another segment, i.e. the trajectory visits the same region of the state space at different times. The direction of these diagonal structures can differ. The longest pronounced diagonal line is called the line of identity (LOI) which gives the recurrence of the trajectory point compared to itself. Diagonal lines parallel to the line of identity (LOI) represent the parallel running of trajectories for the same time evolution. The diagonal structures perpendicular to the LOI represent the parallel running trajectories with contrary times. In order to give the reader a taste of information RPs can provide we have depicted in figures 3(a)–(c) RPs for three typical scenarios. RPs of a sine wave (figure 3(a)), uniformly distributed, independent noise (figure 3(b)), and the chaotic Lorenz system (figure 3(c)) show very different recurrence patterns. The RP of the uncorrelated stochastic signal shows the typical salt and pepper pattern for such a signal. While the RP for the periodic motion shows a series of equally spaced long and uninterrupted lines that are parallel to the diagonal, the orthogonal distances between these lines correspond to the period of the oscillation. The RP for the chaotic Lorenz system also shows diagonals which are however seemingly shorter. There are also certain orthogonal distances between them, which are however not as regular as in the case of the periodic motion.
The localization and quantification of unstable periodic orbits (UPOs) in chaotic attractors is very important, since the orbit on a chaotic attractor is the closure of the set of UPOs. Roughly speaking, a trajectory, therefore, can be regarded as jumping from one UPO to the next one. RPs can be used to easily localize UPOs in chaotic time series (Bradley and Mantilla 2002). The main idea is the following: when the trajectory of the system comes close to an UPO, it stays in its vicinity for a certain time interval, whose length depends on how unstable the UPO is. This is reflected in the RP, as the pattern corresponding to periodic movement consists of uninterrupted equally spaced diagonal lines.

A crucial parameter to be chosen is the value of \( \varepsilon \). If \( \varepsilon \) is chosen too small, there may be almost no recurrence points and we cannot learn anything about the recurrence structure of the underlying system. On the other hand, if \( \varepsilon \) is chosen too large, almost every point is a neighbour of every other point, which leads to a lot of artefacts. A too large \( \varepsilon \) also includes points in the neighbourhood that are simple consecutive points on the trajectory. This effect is called tangential motion and causes thicker and longer diagonal structures in the RP as they actually are. Hence, one has to find a compromise for the value of \( \varepsilon \). Many methods have been advocated in the literature for the calculation of \( \varepsilon \) (Zbilut et al 2002, Thiel et al 2002, Schinkel et al 2008). One possibility is to choose \( \varepsilon \) to be a few percent of the state space diameter (Schinkel et al 2008). Alternatively, one can choose \( \varepsilon \) such that it takes account of the fact that any measurement of a process is a composition of the real signal and some measurement noise of a given standard deviation (Thiel et al 2002). In this study, to allow for a consistent representation of the RPs for the 16 patients considered \( \varepsilon \) has been chosen of the order of the standard deviation of the distribution of the measurement noise for the population, which did yield a value of \( \varepsilon = 0.3 \).

3. Results

3.1. Pre-processing of breathing samples

In order to explore if lung patient’s breathing patterns demonstrate a sensitive dependence on initial conditions, i.e. are chaotic in nature, all parameters as explained in section 2 were calculated for all 16 patients including the sample patient, but keeping the length of the paper limited pictorial results are only shown for the sample patient. For all the patients a time series representing the lung cancer patient breathing patterns was obtained using RPM™. The presence of a linear trend was observed in the recorded respiratory data. Clearly, this
cannot be attributed to any physiological process and this is purely due to a drift of the measurement system. A linear detrending process was applied to this data by simply fitting a best-fit line through the data and then subtracting the trend to finally obtain a detrended time series signal. This is illustrated in figure 4. Signals were normalized such that the max peak-to-peak amplitude is equal to unity. No further measurement noise reduction techniques were employed.

3.2. Time delay calculation

A proper time delay $\tau$ was found based on Fraser and Swinney’s mutual information function methodology (Fraser and Swinney 1986). The mutual information function was calculated using the TSTOOL package available under Gnu Public License (GPL). Mutual information plotted as a function of delay in samples for the sample patient is shown in figure 5. For the sample patient, the first local minimum is obtained at delay equal to 49 samples. The delay parameter $\tau = 49$ was used for reconstruction of the embedding state space plot.

3.3. Embedding dimension calculation

Another essential parameter for reconstruction of the state space plot, the minimal embedding dimension $m$ that allows one to disentangle the attractor was estimated based on the FNN method. The results obtained with the FNN method for the sample patient are shown in figure 6. It can be seen that the percentage of the FNN convincingly drops to zero for $m = 5$ and hence a minimal embedding dimension equal to 5 is appropriate for the respiratory signal under consideration. The embedding dimension obtained for the other patients is shown in table 1. As can be seen from table 1 the embedding dimension across patients varies from 4 to 6, indicating that human breathing could have active degrees of freedom that vary within
Figure 5. The mutual information value as a function of delay time is shown here. The optimal time delay is selected as the first local minimum of the mutual information function. For the sample patient presented here, the delay time is equal to 49 samples.

Table 1. Scalar time series acquisition time \(t\), delay time \(\tau\), embedding dimension \(m\), stationarity (min, max and average), determinism factor \(k\) and largest Lyapunov exponent (LLE) calculated for the breathing pattern of all the patients is tabulated above.

<table>
<thead>
<tr>
<th>Patient number</th>
<th>(t)</th>
<th>(\tau)</th>
<th>(m)</th>
<th>Min</th>
<th>Max</th>
<th>Avg</th>
<th>(k)</th>
<th>LLE</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>316.67</td>
<td>35</td>
<td>5</td>
<td>0.8026</td>
<td>1.4320</td>
<td>1.0563</td>
<td>0.964</td>
<td>0.2394</td>
</tr>
<tr>
<td>2</td>
<td>110.57</td>
<td>53</td>
<td>6</td>
<td>0.9080</td>
<td>1.1161</td>
<td>0.9974</td>
<td>0.972</td>
<td>0.1731</td>
</tr>
<tr>
<td>3</td>
<td>107.70</td>
<td>30</td>
<td>5</td>
<td>0.7203</td>
<td>1.2211</td>
<td>0.9968</td>
<td>0.973</td>
<td>0.2783</td>
</tr>
<tr>
<td>4</td>
<td>130.00</td>
<td>38</td>
<td>6</td>
<td>0.908</td>
<td>1.0842</td>
<td>0.9921</td>
<td>0.979</td>
<td>0.2169</td>
</tr>
<tr>
<td>5</td>
<td>103.3</td>
<td>45</td>
<td>6</td>
<td>0.7954</td>
<td>1.2464</td>
<td>0.9905</td>
<td>0.977</td>
<td>0.1823</td>
</tr>
<tr>
<td>6</td>
<td>189.43</td>
<td>43</td>
<td>5</td>
<td>0.8999</td>
<td>1.2344</td>
<td>1.0038</td>
<td>0.969</td>
<td>0.2269</td>
</tr>
<tr>
<td>7</td>
<td>143.80</td>
<td>30</td>
<td>5</td>
<td>0.9139</td>
<td>1.1163</td>
<td>1.0046</td>
<td>0.992</td>
<td>0.2266</td>
</tr>
<tr>
<td>8</td>
<td>184.23</td>
<td>32</td>
<td>5</td>
<td>0.8701</td>
<td>1.0958</td>
<td>0.9890</td>
<td>0.967</td>
<td>0.2961</td>
</tr>
<tr>
<td>9</td>
<td>72.60</td>
<td>39</td>
<td>5</td>
<td>0.9158</td>
<td>1.1053</td>
<td>1.0257</td>
<td>0.974</td>
<td>0.2402</td>
</tr>
<tr>
<td>10</td>
<td>119.30</td>
<td>41</td>
<td>4</td>
<td>0.8599</td>
<td>1.2169</td>
<td>1.0071</td>
<td>0.994</td>
<td>0.2000</td>
</tr>
<tr>
<td>11</td>
<td>235.97</td>
<td>82</td>
<td>4</td>
<td>0.8857</td>
<td>1.0189</td>
<td>0.9380</td>
<td>0.996</td>
<td>0.1088</td>
</tr>
<tr>
<td>12</td>
<td>53.00</td>
<td>40</td>
<td>4</td>
<td>0.9246</td>
<td>1.0539</td>
<td>1.0067</td>
<td>0.985</td>
<td>0.3046</td>
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<tr>
<td>13</td>
<td>173.73</td>
<td>29</td>
<td>5</td>
<td>0.9350</td>
<td>1.1247</td>
<td>1.0065</td>
<td>0.987</td>
<td>0.3294</td>
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<tr>
<td>14</td>
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<td>28</td>
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<td>0.8606</td>
<td>1.1422</td>
<td>1.0068</td>
<td>0.979</td>
<td>0.2615</td>
</tr>
<tr>
<td>15</td>
<td>138.40</td>
<td>25</td>
<td>4</td>
<td>0.9912</td>
<td>1.0096</td>
<td>0.9985</td>
<td>0.999</td>
<td>0.2749</td>
</tr>
<tr>
<td>Sample</td>
<td>194.53</td>
<td>49</td>
<td>5</td>
<td>0.8674</td>
<td>1.1283</td>
<td>1.0011</td>
<td>0.969</td>
<td>0.2119</td>
</tr>
</tbody>
</table>

this range. Therefore a mathematical model for human breathing may require as few as four first-order differential equations or as many as six first-order differential equations depending on the complexity of the breathing pattern.
3.4. Stationarity test

For the sample patient, figure 7 illustrates the cross-prediction errors for all combinations of segments $S_i$ and $S_j$ for the original time series. For all breathing traces considered in this study the average value of $\delta(i, j)$ is 1.01, while the minimum and maximum RMS cross-prediction errors are 0.87 and 1.13, respectively. As can be seen from table 1 for all breathing traces we have considered the maximum and minimum cross-prediction errors differ by less than a factor of 2 from each other as well as the average cross-prediction error. It has been observed by others (Perc 2005) that if for a given time series the maximal cross-prediction error is less than twice the average prediction error and if all cross-prediction errors differ by no more than a factor of 2, then the time series can be considered as stationary. This is the case for all breathing time series we have considered in this study (cf table 1).

3.5. Determinism test

For the sample patient’s time series, (last entry in table 1), the vector field depicting the determinism test for the state space plot shown in figure 2 is displayed in figure 8. The corresponding determinism factor is 0.969. The determinism factors for the other 15 patients are shown in table 1. The factors varied from 0.965 to 0.99. This indicates that the time series under study are generated from an underlying dynamics that is deterministic rather than stochastic in nature.

3.6. Largest Lyapunov exponent calculation

The LLE was calculated using the algorithm as explained earlier. Figure 9 shows a plot of natural logarithm of divergence versus time in seconds. LLE is calculated as the slope (via the least-squares ‘polyfit’ command in Matlab$^\text{TM}$ from MathWorks Inc.) of the linear portion
of the curve. For each breathing signal the algorithm of Rosenstein and colleagues was used to calculate the LLE, and this was accomplished using the L1D2 program by Rosenstein. The results of our calculations are summarized in table 1 for 15 patients. LLE were also positive using Wolf’s method showing the consistency between the two methods. Figure 10 shows the LLE calculated using Wolf and Rosenstein’s algorithms. Wolf’s method was implemented using the TSTOOL package. It is clear that both algorithms yielded a positive LLE for all patients indicating that their breathing pattern is indeed chaotic.

3.7. Recurrence plots

To compute the RPs of a breathing pattern, unthresholded recurrence plots (UTRP) were first generated for the time series after reconstructing the state space plot using the parameters displayed in table 1. Thresholded recurrence plots (TRP) were then computed by thresholding the UTRP by setting the threshold \( \varepsilon = 0.3 \) as explained in section 2.5. Fifteen hundred sample points were used for the calculation of the UTRP and the first 100 points were excluded to eliminate possible transients. The TRP for the breathing pattern of all 15 patients are shown in figure 11. The presence of diagonals indicates that the system under study is highly deterministic. Eckmann and Ruelle (1985) have shown that the length of these short upward diagonal lines is inversely proportional to the Lyapunov coefficients. In figures 11(k) and (o), one can see very strong and continuous diagonals showing that the breathing pattern for those patients is nearly periodic. Bands of white space can be seen in figures 11(g), (j), (l) and (n), which are due to the presence of transients in the time series. In figures 11(g), (l) and (n),
Figure 8. For the sample patient the embedded space was coarse grained into a $10 \times 10 \times 10 \times 10 \times 10$ grid. For each box, the direction of the unit vector was determined using the state space point where the trajectory first enters the box and the point where the trajectory leaves the box. The vector field corresponding to embedding space is presented here in two dimensions.

a small rectangular patch can be seen in parts of the RP, which rather looks like the RP of a periodic motion. This indicates the presence of UPOs as explained in section 2.5

4. Discussion and conclusion

In this work, we have applied methods from nonlinear dynamical system theory to breathing patterns of patients with lung tumours and have found that all breathing patterns considered result from an underlying stationary deterministic dynamical system that exhibits a sensitive dependence on initial condition, i.e. is chaotic by nature. Our analysis has also revealed that the number of first-order differential equation needed to model breathing may depend on the complexity of the breathing pattern a patient exhibits since we found the embedding dimensions to range from 4 to 6 when employing the FNN method, indicating that the active degrees of freedom for the dynamical system underlying the breathing pattern range from 4 to 6.

It is our ultimate hope that these methods will be of value in the further investigation of the open-ended problem of lung tumour motion. Variations in the breathing pattern, during the course of treatment, are a major cause of changes in intrafraction tumour motion trajectory. In this study we have presented findings and evidence based on well-proven nonlinear time series analysis methods that the breathing pattern of lung cancer patients is not random or irregular (as stated in several studies mainly in the radiotherapy related literature), rather that it is deterministic in nature albeit chaotic. Our main emphasis in this study has been to establish the fact that in order to establish the chaotic nature of time series associated with the
breathing patterns of lung cancer patients, one first has to check that the data originate from a stationary and deterministic process. Stationarity of data was established employing the nonlinear statistics of cross-prediction error. For determinism, an attractor was reconstructed.

Figure 9. Average logarithmic divergence versus time is displayed in this graph. The slope of the logarithmic relation represents the LLE ($\lambda_{\text{max}}$).

Figure 10. Largest Lyapunov exponent calculated for all patients using Wolf’s and Rosenstein’s algorithm is shown here. As can be seen from the figure above both methods yield a positive value for the largest Lyapunov exponent.
Figure 11. Recurrence plots for the breathing pattern of 15 patients under study (a)–(o) and for the sample patient (p) is presented here.

Based on the appropriate time delay ($\tau$) and embedding dimension ($m$) using the mutual information method (Fraser and Swinney 1986) and the FNN method (Kennel et al 1992), respectively. An average value of 0.97 for the determinism factor across all patients clearly indicates that the underlying dynamical system describing breathing is not of a stochastic nature. Once these criteria are met, the calculation of invariant quantities such as maximal LE is appropriate to characterize the dynamics of the given dynamical system. Hence, the existence of positive Lyapunov coefficients shows that the attractor in the time series signal under consideration exhibits a sensitive dependence on initial conditions, and is convincing evidence for the presence of chaos in the studied time series.

There are several new aspects that are particular to dynamical system theory, namely the geometrical view of the temporal behaviour of the underlying dynamical system and the existence of ‘topological characteristics’, such as its dimension, as well as ‘dynamical
characteristics’ such as the existence of positive LEs, i.e. its sensitive dependence on initial conditions which are persevered under time delay embedding.

Recognizing and quantifying chaos in time series is an important step in understanding the behaviour of the higher dimensional time series from a physiological system. Currently, many research groups have developed prediction engines and depending on the robustness and accuracy of the prediction method, the error in prediction due to the inherent characteristic of sensitive dependence on initial conditions can be estimated. This then can then be used to find an estimate of how far into the future could one predict chaotic signals accurately, i.e. the prediction horizon. Theoretically, a prediction engine based on chaotic dynamics can predict better than other methods provided an appropriate time delay and an embedding dimension are chosen allowing one to reconstruct an attractor in which FNN that can lead to incorrect prediction are not present. In fact this will be the major theme of our future work.

The work presented in this paper can be extended in several ways for tracking tumour motion in real time. One can, for example, model a breathing pattern based on neurophysiologic mechanisms. Another possibility is to establish a correlation function between breathing pattern and actual tumour motion and using tools from nonlinear system theory to dynamically model and predict tumour motion, which can then be used for real-time tracking of the tumour and other tumour motion management methodologies. Lastly, unique RPs shown in this work corresponding to breathing patterns of each patient can be used to improve the major issue of duty cycle of well-established gating methodologies for treating mobile tumours.

So, whenever one deals with breathing patterns or tumour motion of lung cancer patients, taking into account the nonlinear time series, analysis shown in this work may provide a valuable adjunct to linear statistical analysis of apparently random looking time series. Chaotic signals possess infinite memory because the effect of past values never dissipates.

It is of importance to note that the idea of using delay coordinates in time series modelling is nothing new. Yule (1927) used an autoregressive (AR) model (which is a delay coordinate representation using a linear model) to formulate a predictive model for the sunspot cycle. Delays, derivatives, principal component analysis and a variety of other methods have been widely used in time series analysis and some of these methods have also been used in tumour motion management in radiotherapy. In this work, effort has been put forth to join the findings of previous works related to tumour motion management with new aspects of dynamical system theory.

It is thus important to understand the respiratory signal from a new perspective by considering breathing as a nonlinear dynamical system. Thus, this work may help in designing patient-specific advanced 4D treatment methodologies based on their day-to-day breathing pattern.

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